PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SCHWEGMAN, LUNDBERG, WOESSNER
& KLUTH P.A.
Attn. Steffey, Charles E.
P.O. Box 2938
Minneapolis, MN 55402
UNITED STATES OF AMERICA

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 31.03.06
Applicant's or agent's file reference 341.034WO1	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2005/033218	International filing date *(day/month/year)* 16/09/2005
Applicant PROMEGA CORPORATION	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Christian Pozzi

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
341.034WO1		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2005/033218	16/09/2005	17/09/2004
Applicant		
PROMEGA CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 9 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/033218

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] on paper

   [X] in electronic form

   c. time of filing/furnishing

   [X] contained in the international application as filed

   [X] filed together with the international application in electronic form

   [ ] furnished subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/033218

A. CLASSIFICATION OF SUBJECT MATTER
C12N15/09 C12N15/31

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/23541 A (ALEXION PHARMACEUTICALS, INC; FODOR, WILLIAM, L; RAMSOONDAR, JAGDEECE,) 5 April 2001 (2001-04-05) * There is 94,521% identity in 803 nt overlap (total 825 nt) of the sequence shown in Fig. 4 with SEQ ID NO: 4 of the present application *	11,15
A	WO 2004/042010 A (UNIVERSITY OF TENNESSEE RESEARCH FOUNDATION) 21 May 2004 (2004-05-21)	
A	US 5 670 356 A (SHERF ET AL) 23 September 1997 (1997-09-23) cited in the application	
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2006	31.03.06

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hillenbrand, G

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/033218

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/100076 A1 (GARCON FREDERIC ET AL) 25 July 2002 (2002-07-25) * There is 88,19% identity of SEQ ID NO: 2 in 906 nt overlap (total 5909 nt) with SEQ ID NO: 74 (1252 nt) of the present application - 39,2% identity of SEQ ID NO: 2 to SEQ ID NO: 41 *	47,49,50
X	WO 97/08320 A (MORPHOSYS GESELLSCHAFT FUER PROTEINOPTIMIERUNG MBH; KNAPPIK, ACHIM; PA) 6 March 1997 (1997-03-06) * There is 88,19% identity of the sequence of Fig. 36 in 906 nt overlap (total 1289 nt) with SEQ ID NO: 74 (1252 nt) of the present application - 39,2% identity of SEQ ID NO: 2 to SEQ ID NO: 41 *	47,49,50
X	DATABASE EMBL 1 March 1996 (1996-03-01), GROSKREUTZ ET AL.: "Cloning vector pGL3-Basic, complete sequence" XP002371236 retrieved from EBI Database accession no. U47295 * There is 85,82% identity of U47295 in 3095 nt overlap (total 4818 nt) with SEQ ID NO: 89 (4333 nt) of the present application * abstract	63-67
X	DATABASE EMBL 15 May 2001 (2001-05-15), ZHUANG, Y. ET AL.: "Co-reporter vector phRG-B, complete sequence" XP002371237 retrieved from EBI Database accession no. AF362550 * There is 98,82% identity of AF362550 in 2375 nt overlap (total 4101 nt) with SEQ ID NO: 90 (3522 nt) of the present application * abstract	63-67

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-10, 12-14, 16-30, 32-46, 48, 53, 55-62, 68-69

The present application contains 69 claims, of which 7 claims are independent. They are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Article 6 PCT, as they erect a smoke screen in front of the skilled reader when assessing the intended scope of protection. In view of the fact that the starting (parent) nucleic acid sequences are not defined in most claims, it is impossible for the skilled reader to determine the subject-matter for which protection is sought.The non-compliance with the substantive provisions of the PCT is to such an extent, that a meaningful search of the claims identified above was not possible.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/033218

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 1-10, 12-14, 16-30, 32-46, 48, 53, 55-62, 68-69
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

11 and 15 (partially), 47, 49 and 50 (partially), 63-67 (partially)

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Inventions 1-20 : claims 11 and 15 (partially)

The subject-matter of this group of different inventions comprises an isolated nucleic acid molecule comprising a synthetic nucleotide sequence having a coding region for a selectable polypeptide, wherein the synthetic nucleotide sequence has 90% or less nucleic acid sequence identity to a parent nucleotide encoding a corresponding selectable polypeptide, wherein the nucleotide sequence encodes a selectable polypeptide with at least 85% amino acid sequence identity to the corresponding selectable polypeptide encoded by the the parent nucleotide sequence - wherein the synthetic nucleotide sequence comprises an open reading frame in SEQ ID NO: 4 to SEQ ID NO: 84 as claimed in claims 11 and 15.

Invention 21: claim 31 (partially)

The subject-matter of this invention comprises an isolated nucleic acid sequence encoding a firefly luciferase, wherein the synthetic nucleotide sequence has 80% or less nucleic acid sequence identity to a parent nucleotide having SEQ ID NO: 43 or 85% or less nucleic acid sequence identity to a parent nucleic acid sequence having SEQ ID NO: 14 which encodes a firefly luciferase, wherein the nucleotide sequence encodes a firefly luciferase with at least 85% amino acid sequence identity to the corresponding luciferase encoded by the the parent nucleotide sequence, wherein the synthetic nucleotide sequence comprises an open reading frame in SEQ ID NO: 21-23.

Invention 23: claims 47, 49 and 50 (partially)

A plasmid comprising SEQ ID NO: 74 which comprises an open reading frame with less than 90% nucleic acid sequence identity to 41 which confers resistance to ampicillin.

Inventions 24-46: claims 51-52 (partially)

A polynucleotide which hybridizes under stringent hybridization conditions to SEQ ID NO: 4 to SEQ ID NO: 23 as claimed in claim 51 and encodes a selectable polypeptide or a firefly luciferase.

Invention 47: claim 54

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

An isolated nucleic acid molecule comprising a synthetic nucleotide sequence which does not code for a desirable peptide or polypeptide but includes sequences which inhibit transcription and/or translation wherein the synthetic nucleotide sequence has SEQ ID NO: 49.

Inventions 48-49: claims 63-67 (partially)

A plasmid which includes a sequence including SEQ ID NO : 89 or SEQ ID NO: 90.
The search was limited to matter related to invention 1 and inventions 23, 48 and 49 as requested by the applicant in his letter dated 13.02.2006.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/033218

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0123541 A	05-04-2001	AU 7744800 A	30-04-2001
		CA 2385162 A1	05-04-2001
		EP 1220928 A2	10-07-2002
		JP 2003510072 T	18-03-2003
		MX PA02003232 A	22-09-2003
WO 2004042010 A	21-05-2004	AU 2003301883 A1	07-06-2004
US 5670356 A	23-09-1997	NONE	
US 2002100076 A1	25-07-2002	AT 306553 T	15-10-2005
		BR 0104564 A	04-06-2002
		EP 1186666 A2	13-03-2002
		FR 2812883 A1	15-02-2002
WO 9708320 A	06-03-1997	AT 219517 T	15-07-2002
		AU 725609 B2	12-10-2000
		AU 6874596 A	19-03-1997
		CA 2229043 A1	06-03-1997
		DE 69621940 D1	25-07-2002
		DE 69621940 T2	16-01-2003
		DK 859841 T3	09-09-2002
		ES 2176484 T3	01-12-2002
		JP 2001519643 T	23-10-2001
		PT 859841 T	29-11-2002
		US 6300064 B1	09-10-2001

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/033218	16.09.2005	17.09.2004

International Patent Classification (IPC) or both national classification and IPC
C12N15/09, C12N15/31

Applicant
PROMEGA CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

D- 06/30/06
RESP. DUE

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hillenbrand, G Telephone No. +49 89 2399-8428

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-10, 12-14, 16-46, 48, 51-62, 68-69

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-10, 12-14, 16-46, 48, 51-62, 68-69

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 11, 15 (partially), 47, 49-50 (partially), 63-67 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11, 47, 49-50, 63-67 (all partially)
	No:	Claims	15 (partially)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	11,15, 47, 49-50, 63-67 (all partially)
Industrial applicability (IA)	Yes:	Claims	11,15, 47, 49-50, 63-67 (all partially)
	No:	Claims	

2. Citations and explanations

   see separate sheet

D1: WO 01/23541 A (ALEXION PHARMACEUTICALS, INC; FODOR, WILLIAM, L; RAMSOONDAR, JAGDEECE,) 5 April 2001 (2001-04-05)

D2: US 2002/100076 A1 (GARCON FREDERIC ET AL) 25 July 2002 (2002-07-25)

D3: WO 97/08320 A (MORPHOSYS GESELLSCHAFT FUER PROTEINOPTIMIERUNG MBH; KNAPPIK, ACHIM; PA) 6 March 1997 (1997-03-06)

D4: DATABASE EMBL 1 March 1996 (1996-03-01), GROSKREUTZ ET AL.: "Cloning vector pGL3-Basic, complete sequence" XP002371236 retrieved from EBI Database accession no. U47295

D5: DATABASE EMBL 15 May 2001 (2001-05-15), ZHUANG, Y. ET AL.: "Co-reporter vector phRG-B, complete sequence" XP002371237 retrieved from EBI Database accession no. AF362550

Re Item IV

Lack of unity of invention

The present application does not meet the requirements of Rule 13 PCT. The detailed reasons for this opinion have already been given in the International Search Report. This authority has identified 49 different inventions which are not so linked to each other as to form a single general novel and inventive concept. Since the applicant has paid additional fees **the search and examination has been carried out for inventions 1, 23, 48 and 49, i.e. matter related to SEQ ID NO: 4, 74, 89 and 90.**

General remarks

Pursuant to Rule 13 (1) PCT the International application shall relate to one invention only or to a group of inventions so linked as to form a single general novel and inventive concept. With respect to a group of inventions claimed in an international application, unity of invention exists only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features, i.e. those features which define a contribution which each of the

claimed inventions as a whole makes over the prior art (Rule 13 (2) PCT.

According to the PCT International Search and Examination Guidelines, Chapter 10, 10.17 (pages 78-79) in case of so-called "markush grouping", unity of invention should be considered to be present only when all the alternatives are of similar nature. When the Markush grouping is for alternatives of chemical compounds (like nucleic acid molecules or polypeptides), they should be regarded as being of similar nature where:

(i) all alternatives have a common property or activity, and

(ii) a common structure is present, i.e. a significant structural element is shared by all of the alternatives.

The words "significant structural element is shared by all of the alternatives" refers to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of the existing prior art, and the common structure is essential to the common property or activity (i.e. the sugar-phosphate backbone can never be considered a significant structural element, since it is shared by all known nucleic acid molecules - it would only represent a trivial feature).

Detailed lack of unity reasoning concerning the present application

The present application lacks unity within the meaning of Article 13 PCT because it comprises 49 separate inventions or groups of inventions which are not so linked together as to form a single general novel and inventive concept (see the different groups listed above). The present application concerns (modified) polynucleotides comprising a coding region for a selectable polypeptide.

In the light of the cited prior art, the underlying problem to be solved by the present application is seen in the provision of (further) compounds (nucleic acid molecules) having a coding region for a selectable (modified) polypeptide. The problem is solved by providing the structurally completely different polynucleotides listed in the claims.

With regard to the cited prior art the common special technical feature among the

different identified groups of inventions seems to be the fact that all structurally different polynucleotides claimed encode selectable polypeptides. However, as shown by documents D1, WO2004/7042010 and US 5670356, polynucleotides encoding (modified) selectable polypeptides were already known to the skilled person. D1 discloses already in Fig. 4 a polynucleotide encoding a selectable polypeptide which has 94,251% identity (total 825 nt) with SEQ ID NO: 4 of the present application, whereas the mentioned other two documents disclose modified polynucleotides encoding luciferase. Thus, the single general concept as defined above lacks novelty and/or inventive activity with respect to the cited prior art (lack of unity a posteriori). In view of the multiplicity of structurally completely different polynucleotides proposed as solutions to the technical problem posed and the fact that in the light of the prior art no other technical feature could be identified as being new and common to the identified problem and corresponding solution(s), the ISA is of the opinion that the present application lacks unity of invention.

In addition, it is the position of the ISA that although the 49 different nucleic acid sequences claimed encode polypeptides having a common function (being selectable) they do not posses the required common structure, i.e. a significant structural element shared by all of the alternatives. Thus, even in the absence of any relevant prior art document (which is not the case here), the above mentioned requirements for unity of invention has not been met and the application also lacks unity of invention a priori.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Article 33.2 PCT) and inventive step (Article 33.3 PCT)

Invention 1: matter related to SEQ ID NO: 4 - claims 11 and 15 (partially)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 (partially) is not new in the sense of Article 33(2) PCT. Document **D1** discloses already in Fig. 4 an isolated nucleic acid molecule which has at least 90% nucleotide sequence identity to an open reading frame in SEQ ID NO: 4.

The subject-matter of claim 11 (partially) appears to be novel. However, the subject-matter of claim 11 lacks the required inventive step since it is absolutely unclear which technical problem SEQ ID NO: 4 solves and which surprising/advantageous properties over the known prior art (see **D1**-Fig. 4) are exhibited by SEQ ID NO: 4, which sequence shows a very high identity to the sequence of Fig. 4 in D1.

Invention 23: matter related to SEQ ID NO: 74 - claims 47 and 49-50 (partially)

The subject-matter of claims 47 and 49-50 appears to be novel but lacks the required inventive step in view of documents **D2 and D3**. Both documents disclose already a DNA sequence with very high identity to SEQ ID NO: 74 (please see the data given in the search report) and which confers resistance to ampicillin. In the absence of any surprising/advantageous properties of the claimed sequence over the cited prior art sequences SEQ ID NO: 2 (**D2**) or the sequence of Fig. 36 (**D3**) no inventive activity is seen by the authority.

Invention 48: matter related to SEQ ID NO: 89 - claims 63-67 (partially)

The subject-matter of claims 63-67 appears to be novel but lacks the required inventive step in view of document **D4**. D4 discloses already a DNA sequence with very high identity to SEQ ID NO: 89 (please see the data given in the search report) which sequence encodes at least one selectable and/or screenable polypeptide. In the absence of any surprising/advantageous properties of the claimed sequence over the cited prior art sequence U47295 (**D4**) no inventive activity is seen by the authority.

Invention 49: matter related to SEQ ID NO: 90 - claims 63-67 (partially)

The subject-matter of claims 63-67 appears to be novel but lacks the required inventive step in view of document **D5**. D5 discloses already a DNA sequence with very high identity to SEQ ID NO: 90 (please see the data given in the search report) which sequence encodes at least one selectable and/or screenable polypeptide. In the absence of any surprising/advantageous properties of the claimed sequence over the cited prior art sequence AF362550 (**D5**) no inventive activity is seen to be involved with the claimed matter.